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Data Article

Pharmacokinetic data of synthetic cathinones in female Sprague-Dawley rats

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ABSTRACT

The synthetic cathinones methylone, butylone, and pentylone differ from each other through the one carbon lengthening of the α -alkyl chain: methylone ($-\text{CH}_3$), butylone ($-\text{CH}_2\text{CH}_3$), and pentylone ($-\text{CH}_2\text{CH}_2\text{CH}_3$) while 3,4-methylenedioxymethamphetamine (MDMA) differs from methylone by a single oxygen atom. Studies with MDMA, suggests that there may be male and female pharmacokinetic and pharmacodynamic differences. In the present study, we present the plasma pharmacokinetic data relative to a 20 mg/kg, subcutaneous doses of methylone, butylone and pentylone in female Sprague-Dawley rats. Briefly, plasma samples were collected via a jugular vein cannula, purified, and analyzed using a HPLC system. While we have previously reported on the consistent relationship between structure and pharmacokinetics of these synthetic cathinones in male, Sprague-Dawley rats (Grecco and Sprague, 2016), this data set suggests that there is no consistent relationship of chemical structure and pharmacokinetics of methylone, butylone and pentylone in female Sprague-Dawley rats. The findings from the present study further emphasize the need for the

Abbreviations: MDMA, 3,4-methylenedioxymethamphetamine; JVC, Jugular Vein Cannula; SMBS, Sodium metabisulfite; EDTA, Ethylenediaminetetraacetic acid; sc, subcutaneous; C_{max} , maximum concentration; T_{max} , time of occurrence of maximum concentration; $\text{AUC}_{0-\infty}$, area under the concentration versus time curve; V_d , volume of distribution; CL_p , plasma clearance

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inclusion of female subjects in the pharmacokinetic studies of synthetic cathinones as it is very possible male-female differences may exist in rodent models.

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Specifications table

Subject area	Pharmacology
More specific subject area	Pharmacokinetics of Drugs of Abuse
Type of data	Table and Figures
How data was acquired	A Shimadzu high performance liquid chromatography (Kyoto, Japan) coupled with an autosampler (model SIL-20AC HT) and diode array detector (model SPD-M20A)
Data format	Processed and Analyzed
Experimental factors	Plasma samples were taken following subcutaneous drug injection, purified, and injected into HPLC to determine drug concentration over time.
Experimental features	Very brief experimental description
Data source location	Bowling Green, Ohio, U.S.
Data accessibility	Data is present in current article.
Related research article	Grecco GG, Kisor DF, Magura, JS, & Sprague JE (2017). Impact of common clandestine structural modifications on synthetic cathinone “bath salt” pharmacokinetics. Toxicology and Applied Pharmacology, 328, 18–24.

Value of the data

- These sex differences in the toxicology and pharmacokinetics of MDMA may extend to synthetic cathinone which are β -keto analogs of MDMA, such as methylone, butylone, and pentylone (Fig 1), but these sex differences have not been empirically determined.
- The current data set provides the first estimates of pharmacokinetic parameter values for methylone, butylone and pentylone in female Sprague-Dawley rats.
- Compared to previous pharmacokinetic studies with methylone, butylone and pentylone in male Sprague-Dawley rats [2,6,7], females demonstrate similar T_{max} , C_{max} , and $AUC_{0-\infty}$. However, the other pharmacokinetic values we assessed in the females did display differences from males.
- The findings from the present study further emphasize the need for the inclusion of female subjects in the pharmacokinetic studies of synthetic cathinones as it is very possible male-female differences may exist in rodent models.

1. Data

The data in Fig. 2 illustrates the plasma concentration versus time profiles for the three synthetic cathinones (20 mg/kg sc.). Pharmacokinetic parameter values determined from synthetic cathinone plasma concentration versus time data are shown in Table 1. For methylone, butylone, and pentylone, C_{max} were observed at the 30-min time point (T_{max}). Pentylone, the most lipophilic drug, demonstrated the highest C_{max} at $5252.55 \pm 130.5 \mu\text{g/L}$ and an $AUC_{0-\infty}$ of $464,469 + 37,307 \mu\text{g/L} \times \text{min}$ which were significantly higher than butylone and methylone ($p < 0.001$ and $p < 0.05$, respectively). The removal

of one or two methyl groups from pentylone (butylone or methylone, respectively) represents a greater than five-fold decrease in C_{\max} and a nearly three-fold decrease $AUC_{0-\infty}$. However, no significant differences in C_{\max} or $AUC_{0-\infty}$ were observed when examining methylone and butylone alone.

Methylone displayed a $t_{1/2}$ of 133.5 ± 18.3 min that was significantly longer than butylone or pentylone ($p < 0.05$). The α -alkyl chain lengthening from methylone to butylone and pentylone significantly decreased the CLp/F with pentylone displaying the lowest CLp/F of 12.3 ± 1.2 mL/min.

2. Experimental design, materials, and methods

2.1. Animals

Jugular vein cannulated (JVC) female Sprague-Dawley rats ($n = 4$; 281.75 ± 8.34 g) were obtained from Envigo (Indianapolis, IN). Animals were housed one per cage (cage size: $21.0 \times 41.9 \times 20.3$ cm) at $24\text{--}25^\circ\text{C}$, maintained on a 12:12 h light/dark schedule and provided ad libitum access to food and water. Animal maintenance and research were conducted in accordance with the eighth edition of the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health. Protocols were approved by the Bowling Green State University Animal Care and Use Committee.

Table 1

Pharmacokinetic estimates of synthetic cathinones in the plasma after subcutaneous administration (20 mg/kg) in female Sprague-Dawley rats ($n = 4$). Parameters were calculated from plasma concentration versus time plots depicted in Fig. 2 with noncompartmental analysis.

Plasma pharmacokinetics			
Drug	Methylone	Butylone	Pentylone
T_{\max} (min) (median)	30	30	30
C_{\max} ($\mu\text{g/L}$)	999.04 ± 56.72	797.72 ± 93.14	$5252.55 \pm 130.5^{***}$
$AUC_{0-\infty}$ ($\mu\text{g/L} \times \text{min}$)	$165,005 \pm 7592^*$	$75,750 \pm 8948$	$464,469 \pm 37,307^*$
$t_{1/2}$ elimination (min)	$133.5 \pm 18.3^*$	50.3 ± 8.3	76.6 ± 8.3
CLp/F (mL/min)	$33.9 \pm 2.1^*$	$77.9 \pm 9.8^*$	$12.3 \pm 1.2^*$
Vd (mL)	6459.4 ± 824.9	5354.2 ± 361.7	$1319.2 \pm 57.5^{**}$

Data are mean \pm S.E.M.

* Indicates significantly different than all other drugs for the pharmacokinetic parameter in that row ($p < 0.05$).

** Indicates significantly different than all other drugs for the pharmacokinetic parameter in that row ($p < 0.01$).

*** Indicates significantly different than all other drugs for the pharmacokinetic parameter in that row ($p < 0.001$).

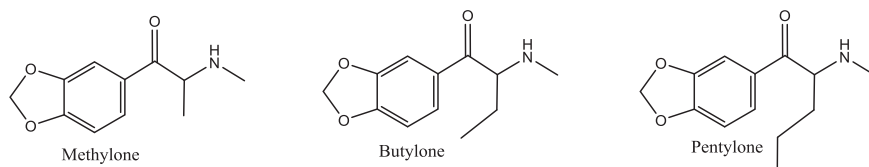


Fig. 1. Chemical structures of the synthetic cathinones examined in this study. These synthetic cathinones differ by lengthening of the α -alkyl chain: methylone ($-\text{CH}_3$), butylone ($-\text{CH}_2\text{CH}_3$), and pentylone ($-\text{CH}_2\text{CH}_2\text{CH}_3$).

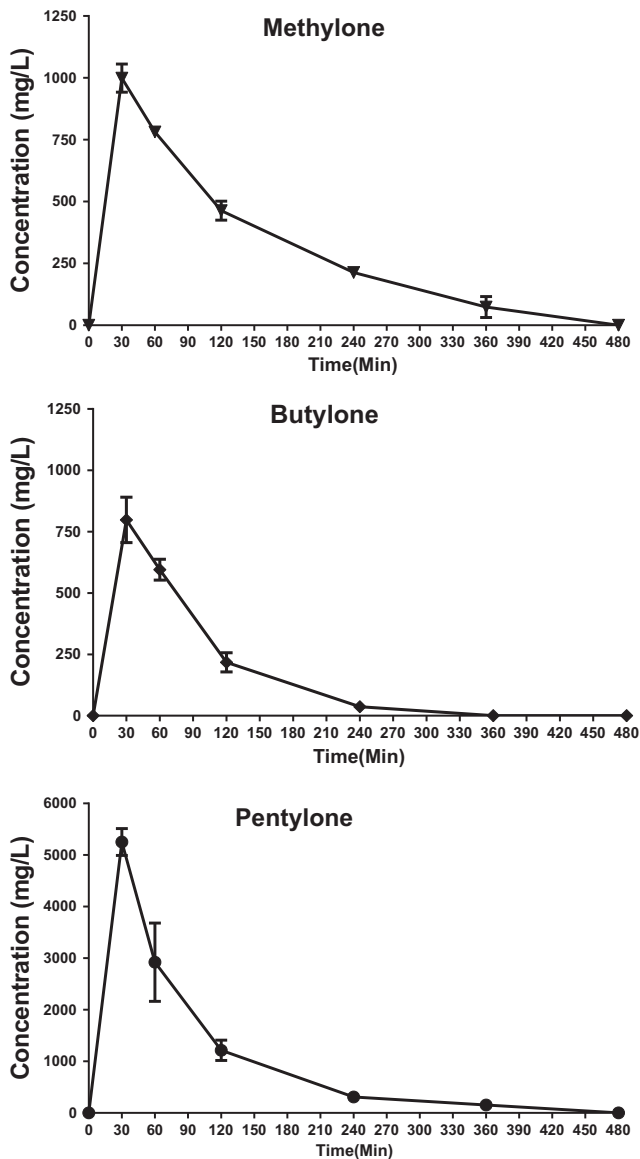


Fig. 2. Plasma concentration versus time plots for synthetic cathinones after subcutaneous administration (20 mg/kg). Female Sprague-Dawley rats ($n = 4$) received synthetic cathinone at time 0. Data are expressed as mean \pm S.E.M.

2.2. Plasma pharmacokinetics study design

We utilized a crossover design following a 7-day washout period after which animals were treated with the next synthetic cathinone at 20 mg/kg, subcutaneous (sc.) based on previous pharmacokinetic and pharmacodynamic studies with these agents [5,6]. Blood samples (250 μ L) were collected at time 0, 30, 60, 120, 240, 360, and 480 min post-treatment. Vaginal lavage was performed prior to treatment to confirm estrous cycle phase using a procedure and criterion outlined elsewhere [4]. At the time of treatment, all animals were determined to be in the diestrus-estrus phase. The plasma purification methods were modified from a previous synthetic cathinone plasma purification method [1]. Briefly,

the blood samples were centrifuged for 5 min at $4100 \times g$ to collect plasma layer and formed elements were discarded. Twenty microliters of 250 mM sodium metabisulfite (SMBS) and $10 \mu\text{L}$ of 250 mM Ethylenediaminetetraacetic acid (EDTA) were added to $100 \mu\text{L}$ of rat plasma and gently vortexed. Protein precipitation was performed with $400 \mu\text{L}$ chilled acetonitrile followed by centrifugation at $9800 \times g$ for 10 min. The supernatant was removed and evaporated to dryness under a stream of nitrogen gas in a 40°C water bath. The remaining solute was reconstituted in mobile phase A (0.1% formic acid in water). The solution was vortexed and centrifuged at $4100 \times g$ for 5 min. The supernatant was then transferred to 1.5 mL autosampler vials containing 0.2 mL glass inserts for injection into HPLC. The synthetic cathinone percent extraction recoveries from these methods varied from 70% to 76%.

2.3. High performance liquid chromatography

A Shimadzu high performance liquid chromatography (Kyoto, Japan) coupled with an autosampler (model SIL-20AC HT) and diode array detector (model SPD-M20A) system was used for quantifying synthetic cathinone concentrations. Chromatographical separation was achieved with a liquid chromatograph (model LC-20AD) using a Kinetex LC column $150 \times 4.6 \text{ mm}$. The gradient elution was performed with mobile phase A (0.1% formic acid in water) and B (0.1% formic acid in acetonitrile) at 0.4 mL/min and 40°C . Synthetic cathinone spiked standards have shown that different percentages and intervals of mobile phase A and B are required for adequate separation of methylone, butylone, and pentylone. For methylone, mobile phase B was maintained for 0.2 min at 10% and increased to 95% over 3 min. Mobile phase B was then held at 95% for 1 min and returned to 10% over 0.5 min. There was a 2 min equilibrium period yielding a total run time of 7 min. For butylone and pentylone, mobile phase B was maintained for 0.2 min at 90% and decreased to 25% over 3 min. Mobile phase B was then held at 25% for 3 min and lowered to 10% over 1 min. There was a 0.5 min equilibrium period yielding a total run time of 7.5 min. All samples were viewed at a wavelength of 290 nm. The drug concentrations of the plasma and CSF samples were calculated using peak-area ratios from standard solutions spiked with synthetic cathinones. The limit of detection for all synthetic cathinones was determined to be $48.83 \mu\text{g/L}$.

2.4. Chemicals and reagents

Racemic methylone, butylone and pentylone were obtained as hydrochloride salts from Cayman Chemical (Ann Arbor, MI). All other reagents were obtained from Fisher Scientific (Hampton, NH). On the day of the study, all drug solutions were made fresh at a concentration of 20 mg/mL in normal saline.

2.5. Pharmacokinetic and statistical analysis

Synthetic cathinone plasma concentration versus time plots (rectangular and semilogarithmic) were constructed, and the data was analyzed using noncompartmental methods using an industry standard software program (WinNonlin Professional 5.1; Pharsight Co., Mountain View, CA) to estimate pharmacokinetic parameter values. The plasma C_{max} was the highest observed plasma concentration and the time of the occurrence of the C_{max} (T_{max}) was also observed. The terminal elimination rate constant (λ_z) was calculated via linear regression of the observed terminal natural log concentration versus time data and $t_{1/2}$ was calculated as $0.693/\lambda_z$. At least three concentration-time points were used to determine λ_z . The volume of distribution (VD) was calculated by the method described by Gibaldi and Perrier [3]. Descriptive pharmacokinetic data is presented as the mean \pm S.E.M. (with exception of the T_{max} which is given as the median value) for each group of animals for each synthetic cathinone. The $\text{AUC}_{0-\infty}$ represents the total area under the plasma concentration-time curve from time zero to infinity, and was calculated using the linear trapezoidal rule with the terminal AUC being calculated as the last measured concentration divided by λ_z (Clast/λ_z). VD was calculated as a ratio of the total dose present in the body to the plasma concentration when the distribution of the drug between the tissues and the plasma is at an equilibrium. The Clp/F corresponds to the plasma

clearance of 9 the drug being calculated as $\text{dose}/\text{AUC}_{0-\infty}$ considering extravascular dosing. GraphPad InStat v.6.0 software was used to complete all statistical analyses of data. Synthetic cathinone pharmacokinetic values were compared using one-way ANOVA with the test drug as the main factor, and in the presence of a significant main effect, a Student–Newman–Keuls post-hoc test was conducted. When only two groups were compared, a Student's *t*-test was used. Significance was set a priori at the 95% confidence level ($p < 0.05$).

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Transparency document. Supplementary material

Transparency document associated with this article can be found in the online version at <https://doi.org/10.1016/j.dib.2018.10.073>.

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